Hyperosmolar Hyperglycemic State

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KEYWORDS

• Hyperglycemia • Hyperosmolar hyperglycemic state
• Hyperosmolar nonketotic state • Diabetic emergency • Endocrine emergency
• Altered mental status

KEY POINTS

- Hyperosmolar hyperglycemic state is defined by the presence of neurologic symptoms or signs in a patient with hyperosmolar, nonketotic, nonacidotic hyperglycemia.
- Patients with HHS have a volume-deficit of up to 9 L, so aggressive volume-repletion is key in the treatment regimen.
- HHS is often triggered by an underlying illness, which must be investigated and addressed concurrently.

INTRODUCTION/HISTORY/DEFINITIONS/BACKGROUND

Hyperosmolar hyperglycemic state (HHS) is a serious and life-threatening diabetic emergency with significant mortality.[1,2] HHS is characterized by altered mental status in the setting of marked hyperglycemia, hyperosmolarity, and dehydration without significant ketoacidosis. HHS has previously been referred to as hyperosmotic hyperglycemic nonketotic state, hyperosmotic hyperglycemic nonketotic coma, and hyperosmotic nonketotic coma. The removal of "coma" from the disease nomenclature represents advances in our understanding of the broader clinical spectrum of this life-threatening illness. Patients with HHS present with varying degrees of mental status alteration, not just coma. Although HHS only accounts for 1% of all primary diabetic admissions,[3,4] its significance as a disease process should not be underestimated. The mortality rate for HHS is 5% to 20%.[4,5] This high degree of mortality is attributed to both the underlying precipitant, as well as advanced age and comorbidity status in those diagnosed. HHS occurs most commonly in adults with type 2 diabetes but is increasingly recognized in children (with type 1 or type 2 diabetes) as well.

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Between 1997 and 2009, the incidence increased by more than 50%.[6] In children, the mortality may be as high as 60%[7]

Diabetic ketoacidosis (DKA) is the quintessential diabetic emergency, and HHS is often described in contrast to it. Although they represent different ends of the spectrum in severity of ketosis and some other clinical features, it is possible for some patients to exhibit overlapping features of both DKA and HHS. **Fig. 1** compares and contrasts features of HHS and DKA.

The pathophysiology of HHS is based on the concomitant effects of hyperglycemia and osmotic diuresis. The inciting event, often an infection, reduces fluid intake in the patient, leading to significant dehydration and volume depletion, followed by dysregulation of glucose balance through a relative reduction in insulin and an increase in counterregulatory hormones. In HHS, insulin levels remain sufficient to inhibit lipolysis and ketogenesis, in contrast to DKA where insulin deficiency results in significant ketogenesis. As glucose concentrations increase in patients developing HHS, the effective serum osmolality increases, worsening osmotic diuresis and dehydration with loss of free water, sodium, and potassium. Volume loss can be significant, up to 9 L. This further exacerbates the glucose concentrations, initiating a spiral of worsening hyperglycemia and volume loss. **Fig. 2** is simplified schematic of the pathophysiology of HHS.

Clinical Presentation

HHS usually develops rather insidiously, during the period of days to weeks. This timeframe contrasts with that of DKA, which commonly develops in a matter of hours to days. Most patients with HHS have a known history of Type 2 diabetes, although for some, HHS will be the first presentation of their diabetes.

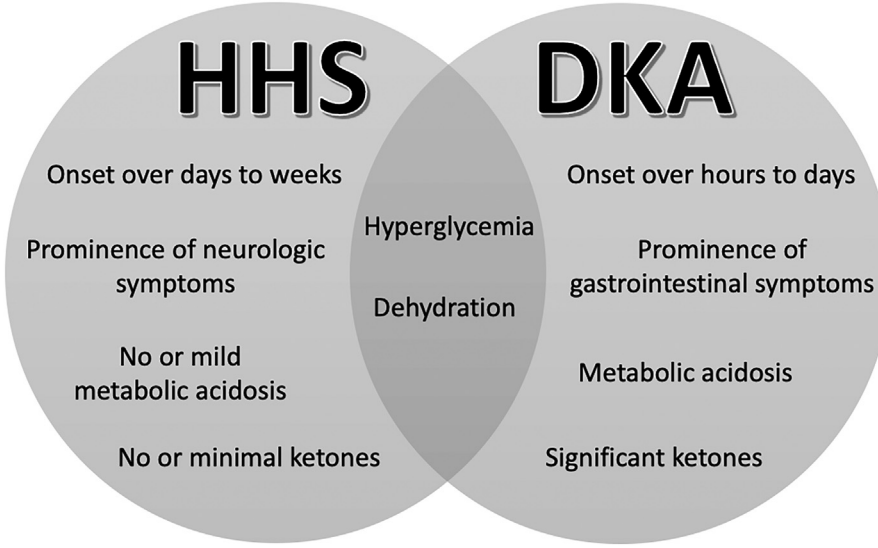

Fig. 1. Features of HHS and DKA. DKA is the quintessential diabetic emergency, and HHS is often described in contrast to it. Although they represent different ends of the spectrum in severity of ketosis and some other clinical features, it is possible for some patients to exhibit overlapping features of both DKA and HHS.

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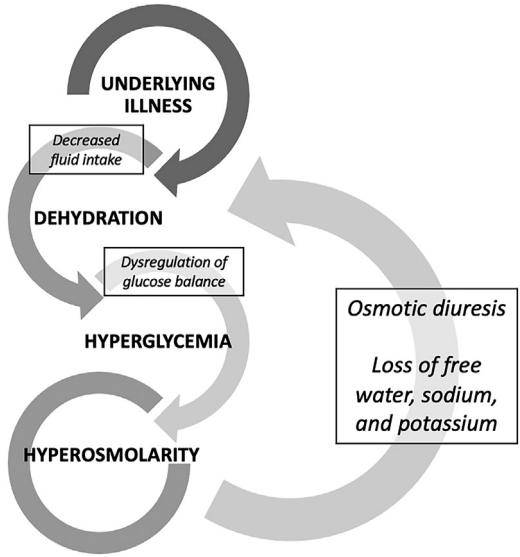

Fig. 2. The pathophysiology of HHS. An underlying illness triggers decreased fluid intake and dehydration, leading to dysregulation of glucose balance and hyperglycemia. The hyperglycemia creates a hyperosmolar state with osmotic diuresis and loss of free water and electrolytes, feeding into the cycle of dehydration and hyperglycemia.

The presenting symptoms of HHS are nonspecific; however, the presence of neurologic symptoms is necessary as part of the diagnosis. These neurologic symptoms present in varying degrees of global or focal neurologic deficits and are attributed to the hyperosmolarity. It is important to note once again that the presentation is not limited to coma but to a spectrum of neurologic changes. Global deficits are most common; these presentations fall along a spectrum, which includes confusion, malaise, somnolence, and other states of altered mental status. Less than one-third of patients present with coma.[4] Patients may present with seizure as their neurologic manifestation, and because of this, HHS must be high on the differential for any patient who presents with seizure and elevated blood glucose levels.

The hyperglycemic state causes symptoms of polyuria, polydipsia, and blurred vision. It also leads to marked osmotic diuresis and volume loss, causing another salient feature of HHS: dehydration. Patients are clinically volume-deplete, with dry mucous membranes, loss of skin turgor, generalized weakness, lightheadedness, orthostasis, and even hypotension and shock.

Care must be taken to actively query and examine for symptoms and signs of infection in patients suspected of having HHS. Although infection is a common underlying cause of HHS, the presence of fever is actually uncommon. This discordance may be explained by the depressed ability for patients with diabetes to mount a fever due to their functionally immunocompromised state. Despite lack of fever, some patients with HHS may still present with symptoms or signs that suggest the underlying infection, such as cough or signs of respiratory failure with pulmonary infection, or skin findings associated with a soft tissue infection.

Other precipitating factors for HHS may contribute to the clinical presentation of a particular patient. Examples would include the presence of chest pain or signs of myocardial dysfunction if an acute coronary syndrome-precipitated HHS, or

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symptoms related to anemia if a gastrointestinal hemorrhage has been complicated by HHS. Gastrointestinal symptoms such as nausea, vomiting, and abdominal pain, are less commonly encountered features of HHS when compared with DKA but when present could be related to the underlying cause.

Diagnosis

Diagnosis is based on the clinical presentation of neurologic symptoms or signs in combination with the laboratory abnormalities described in **Table 1**.

The hallmark laboratory abnormalities of HHS are an elevated blood glucose and an elevated effective serum osmolality without significant ketosis. Previous studies have been able to show a positive linear relationship between serum osmolality and worsening mental status. If a patient has an effective serum osmolality less than 320, then an alternate cause of altered mental status should be pursued.[5,6,8] Although metabolic acidosis is classically associated with DKA rather than HHS, there may be a mild acidosis due to an elevated lactic acid associated with dehydration. In contrast to DKA, these patients do have not have a significant amount of ketone production, although a small number of ketones may be present. The term "Nonketotic" was removed from the name of HHS because it is now understood that small ketones may be present.

In addition to using laboratory evaluation to help confirm the diagnosis of HHS, further testing should be performed in an attempt to reveal a precipitating factor of this diabetic emergency. Although it is certainly possible that this condition may be caused by medication noncompliance or inadequate insulin dosing, other potential causes should be considered and treated appropriately. Most commonly, infections, such as pneumonia or urinary tract infections, act as the metabolic stressor that precipitates HHS, so urinalysis and chest X-ray are recommended as part of the workup.[9] Other stressors, such as trauma or myocardial infarction, can also be the culprit and should be considered as potential causes. Appropriate treatment of these precipitating factors plays an important role in properly treating HHS.

MANAGEMENT

Fluids

The management of HHS is centered on the volume repletion and subsequent lowering of the patient's plasma osmolality. There have not been many recent changes to the treatment algorithm of HHS, and there have been very few high-quality studies to reference while creating treatment guidelines for HHS. Despite this limited evidence, both the American Diabetes Association (ADA) and the Joint British Diabetes

Table 1
Laboratory abnormalities of hyperosmolar hyperglycemic state

Plasma glucose	>600 mg/dL
Effective serum osmolality[a]	>320 mOsm/kg
Arterial pH	>7.30
Serum bicarbonate	>18 mEq/L
Anion gap	Variable
Urine ketones or serum ketones	Trace or small

[a] Effective serum osmolality is defined as 2[measured Na^+ (mEq/L)] + glucose (mg/dL)/18. Notably this calculation does not include urea.

Adapted from consensus statement by the American Diabetes Association.

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Societies for Inpatient Care have published recommended treatment guidelines. For simplicity, this article will predominately focus on the guidelines published by the ADA.

The initial treatment of HHS is predominately driven by volume resuscitation. These patients are typically quite volume depleted from significant polyuria. It is recommended that these patients be given 1000 to 1500 mL or 15 to 20 mL/kg of 0.9% sodium chloride solution during the first hour of their treatment. After the initial fluid bolus, the patient's volume status should be reassessed so that ongoing hypovolemia can be treated appropriately. If the patient does not appear in shock or their hemodynamics have improved, then the patient can be placed on a continuous infusion of fluids rather than receive additional fluid boluses.

Fluid selection continuous infusion is largely based off the patient's corrected serum sodium. This value is calculated by adding 1.6 mg/dL to measured serum sodium for each 100 mg/dL of glucose more than 100 mg/dL[3]. If they have a normal corrected serum sodium or are hypernatremic, it is suggested that the patient be given 0.45% sodium chloride at a rate of 250 to 500 mL/h. If they are hyponatremic, then continued use of 0.9% sodium chloride is suggested. During this infusion, urinary output, respiratory status, and mental status should all be monitored to guide the rate and total amount of volume resuscitation.

Although the ADA consensus statement recommends 0.9% sodium chloride solution as the fluid of choice for the initial resuscitation and then continued 0.9% sodium chloride or switching to 0.45% sodium chloride for the subsequent continuous infusion, it may be reasonable to use an alternative, such as lactated ringers. This might help avoid iatrogenic hyperchloremic metabolic acidosis, particularly with large infusions of 0.9% sodium chloride. However, there are no research studies available to demonstrate efficacy in this patient population. Ultimately, fluid selection should be tailored to each individual patient and their corrected serum sodium level to avoid rapid shifts in serum sodium.

ELECTROLYTES

Patients with HHS frequently have electrolyte derangements attributed to osmotic diuresis and subsequent shifts related to osmotic gradients. Similarly to patients with DKA, patients with HHS may present with a potassium ranging anywhere from hypokalemia to hyperkalemia but generally have a total body deficiency.[6,10] The patient's electrolytes should be checked before the initiation of insulin therapy for this reason. As insulin will further shift potassium intracellularly, it may cause severe hypokalemia and induce potentially life-threatening arrhythmia. If the patient's potassium is less than 3.3 mEq/L, then insulin therapy should be withheld until their potassium has been corrected to above this threshold. Although insulin therapy can be started if the patient's potassium is greater than 3.3 mEq/L, the ADA recommends adding 20 to 30 mEq of potassium per each liter of fluid if the serum potassium is 5.0 to 5.2 mEq/L or less. This is done to prevent hypokalemia caused by intracellular shifts during the continuous insulin infusion. Consider lowering this dose if the patient has a history of renal failure and thus is at higher risk of developing hyperkalemia. The serum potassium level should be checked every 2 hours while the patient is receiving intravenous insulin to promptly recognize the development of potentially life-threatening hypokalemia.

Hypomagnesemia is also a common abnormality in patients with HHS. Because magnesium repletion will likely be needed to adequately correct hypokalemia and prevent further renal losses of potassium, a magnesium level should be obtained to help guide treatment.[10] Magnesium replacement may also provide some protection from

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arrhythmia such as torsades de pointes if the patient is developing a prolonged QT from their other electrolyte abnormalities, such as hypokalemia.

Data regarding the treatment of hypophosphatemia in patients with HHS are limited and generally extrapolated from the DKA population. Similar to potassium, total body phosphate levels are generally depleted but the serum phosphate level could initially be elevated or normal. However, it is not recommended that hypophosphatemia be treated until the phosphate level drops to less than 1.0 mg/dL due to concerns that phosphate therapy may prompt precipitation with calcium and cause worsening hypocalcemia.[11] Treatment is also indicated if hypophosphatemia could be contributing to the patient's respiratory depression or muscle weakness. If treatment is indicated, the patient's replacement fluids can be supplemented with 20 to 30 mEq/L of potassium phosphate.[12]

Insulin

Insulin therapy is recommended only after fluid resuscitation in addition to evaluation and appropriate correction of electrolyte deficiencies. Repeat glucose evaluation may reveal a considerable decrease in glucose concentration after intravenous fluids alone. Although the Joint British Diabetes Societies for Inpatient Care does not recommend insulin therapy until glucose levels have plateaued at an elevated level despite ongoing fluid therapy, the ADA does recommend the initiation of insulin therapy. Although previous studies have shown that subcutaneous or intramuscular insulin can be used to treat DKA, similar data does not exist for the treatment of HHS.[13] Regardless for both DKA and HHS, intravenous infusion of regular insulin is preferred over subcutaneous or intramuscular injection because it has a more rapid onset and it is easier to titrate. The current ADA guidelines recommend the same insulin infusion protocol for both HHS and DKA.

The ADA provides 2 different insulin protocols that can be used. This first recommends a bolus of 0.1 units/kg followed by an infusion of 0.1 units/kg/h. The alternative recommended protocol uses a continuous infusion of 0.14 units/kg/h without an initial bolus dose. This recommendation is based on a study that showed no significant difference between these protocols in time to reach a glucose level of 250 mg/dL or lesser, pH 7.3 or greater, and bicarbonate level of 15 mEq/L or greater in patients with DKA.[3] Notably, this study has not been performed in patients with HHS. The ideal target of fluid and insulin therapy is to decrease the blood glucose concentration at a rate of approximately 50 to 75 mg/dL/h. If this target is not reached, then the infusion rate can be increased on an hourly basis until this goal is met. If the serum glucose decreases significantly faster than the goal rate, then consider decreasing the infusion rate to avoid a rapid decrease in osmolality or hypoglycemia. Once a patient's serum glucose decreases to 300 mg/dL, consider decreasing the infusion rate to 0.02 to 0.05 units/kg/h in order to maintain a serum glucose between 250 and 300 mg/dL. Dextrose-containing fluids, such as 5% dextrose, can also be added to the continuous fluid infusion to maintain this glucose concentration. This glucose concentration should be sustained until the patient's HHS has resolved. Resolution of HHS is identified by return to normal mental status along with a normal serum osmolality.

Once the HHS has resolved, the patient can begin the transition to subcutaneous insulin. Ideally, the administration of subcutaneous basal/long-acting insulin takes place 1 to 2 hours before discontinuation of the intravenous insulin infusion.[6,9] This allows time for the onset of action of the subcutaneous insulin to take place while the patient's glucose is still being controlled by intravenous insulin. If this overlap is not provided, the patient is at higher risk of worsening hyperglycemia and recurrent HHS. The transition to subcutaneous insulin should take place when the patient is alert

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and able to eat so that they can avoid hypoglycemia. If they remain nil per os (NPO), consider continuing dextrose-containing IV fluids along with an IV insulin infusion. If the patient already has an insulin regimen as part of their diabetes care, it is appropriate to start with their normal regimen, typically using the basal insulin if they use a basal-bolus regimen and they have not had a dose in the last 24 hours. If they do not already have an insulin regimen, one can be created by calculating a total dose of 0.5 to 0.7 units/kg/d and giving half of the total units once daily as a long-acting insulin, such as insulin glargine. The other half of the units can be divided up equally and given before meals.[9]

Example Insulin Calculation

- For a 100-kg patient using a total daily dose of 0.5units/kg/d, the total insulin use during 1 day is as follows: 100 kg $\times$ 0.5units/kg/d = 50 units/d
- Half of the daily need would be given as basal long-acting, and the other half would be divided with meals, resulting in: 25 units of basal long-acting insulin to be given once a day + approximately 8 units of rapid acting insulin with each meal (assuming 3 meals per day)

COMPLICATIONS

A large portion of the available information about the potential complications of treating HHS is extrapolated from data gathered from treating patients with DKA. With the treatment algorithms being similar, these assumptions are fair; however, it should be noted that data gathered specifically from the HHS population are limited.

Hypoglycemia can occur commonly in the treatment of HHS due to the use of infusions of intravenous insulin and the resources needed to monitor the patient appropriately.[6,9] Hypoglycemia can ultimately lead to seizures, coma, and death if not recognized promptly. Repeat glucose checks should be performed hourly while the patient remains on the insulin infusion so that developing hypoglycemia can be identified early. Treatment includes lowering the insulin infusion rate and starting intravenous dextrose-containing fluids. Additionally, as discussed previously, patients should be alert and able to eat before initiating the transition to subcutaneous insulin.

Hypokalemia is also a common complication that can occur with the insulin infusion. As discussed previously, these patients typically already have low total body potassium, and then the insulin infusion will shift a portion of the patient's remaining potassium intracellularly. This puts them at high risk for hypokalemia and its associated complications, including arrhythmia, respiratory failure, and muscle weakness. The treatment section of this article previously discussed the protocol for insulin initiation and potassium replacement to avoid this complication. Repeat evaluation of electrolytes is recommended every 2 hours.[9]

Volume overload and pulmonary edema are also potential complications associated with treatment of HHS due to the initial large volume fluid resuscitation and continuous intravenous fluids. Frequent reassessment of the patient's volume status and respiratory status should be performed and fluid doses adjusted accordingly. Special consideration should be given to patient populations with an increased risk of volume overload, such as those with congestive heart failure or chronic kidney disease.[8,11,16] There are not specific guidelines for these patient populations but treatment should be tailored to each patient individually based on their unique physiology. Changes in vitals and physical examination, in addition to tools such as bedside ultrasound, may be helpful in guiding treatment. Ultimately, the treatment of HHS may be limited and consequently slower based on their ability to tolerate continued intravenous fluids.[3]

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Development of rhabdomyolysis can also occur in this patient population due to profound dehydration. Symptoms consistent with rhabdomyolysis, myoglobinuria, or worsening renal function should prompt evaluation of creatinine kinase levels.

One of the most feared complications of the treatment of HHS is the development of cerebral edema. Earlier animal models have been able to show that sustained hyperglycemia increases brain osmolality. Development of cerebral edema can then occur when the serum glucose is rapidly lowered using insulin and hypotonic fluids. This rapid decrease in serum glucose creates an osmotic gradient that moves water into the brain.[14] The same study also indicated that the risk of cerebral edema increases once the serum glucose decreases less than 250 mg/dL. Data based on human studies are limited but it is recommended that serum glucose levels be kept more than 250 mg/dL and closer to 300 mg/dL during the treatment of HHS to minimize this risk.[8,15] If cerebral edema does occur, a mannitol infusion is the recommended treatment.

Pediatric Population

HHS is relatively uncommon in the pediatric population, particularly when compared with DKA. There are no prospective data to suggest the best treatment of children with HHS; however, the Pediatric Endocrine Society did publish guidelines for the treatment of children with HHS in 2011.[17] There are minor differences in the treatment guidelines when compared with the recommendations for adults. It is recommended that treatment start with an intravenous fluid bolus of at least 20 mL/kg of 0.9% sodium chloride solution. After that, the remaining deficit should be replaced during 24 to 48 hours using 0.45% to 0.75% sodium chloride solution. These solutions are preferred for continuous infusion to prevent hypernatremia. Intravenous fluids alone can decrease the serum glucose as a rate of 75 to 100 mg/dL/h. Insulin is only started in the pediatric population once the rate of serum glucose decline drops to less than 50 mg/dL/h. If insulin treatment is needed, the initial rate should be 0.025 to 0.5 units/kg/h. Similar complications exist in the pediatric population as in adults and generally have the same treatment approach. Similar to DKA, there is concern that the risk of cerebral edema may be higher in children than in adults. However, there is some evidence that cerebral edema may be less prevalent with the treatment of HHS than DKA. This difference is hypothesized to be related to compensatory hypocapnia causing cerebral vasoconstriction and then subsequent reperfusion with treatment that occurs during with DKA but is not a significant element of HHS.[7]

Disposition

All patients with HHS need hospitalization and further monitoring in the intensive care unit due to their significant altered mental status and high mortality. With the average time to resolution with proper treatment taking approximately 9 to 11 hours, taking care of these patients uses many resources and would be most appropriate in an intensive care setting[4] repeated evaluation of mental status, volume status, vitals, renal function, and blood tests. Serum glucose should be evaluated every hour while the patient is on an insulin infusion, and electrolytes, serum osmolality, and renal function should be checked every 2 to 3 hours.[7] In the setting where the patient is boarding in the emergency department for an extended period, if they have complete resolution of their HHS with successful transition to subcutaneous insulin and multiple hours of observation with normal mental status, it may be reasonable to admit the patient to a non-ICU medical unit.

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SUMMARY

HHS carries high morbidity and mortality but outcomes can be improved with prompt recognition and initiation of treatment. This will entail a thorough investigation of the underlying cause, treatment of fluid resuscitation and insulin, and close monitoring in the hospital.

CLINICS CARE POINTS

- HHS is distinguishable from DKA by little or no ketoacid accumulation and typically higher degree of hyperglycemia (>600 mg/dL but may exceed 1000 mg/dL).
- Diagnosis is typically made from clinical presentation with altered mental status and an effective serum osmolality greater than 320 mOsm/kg in a patient without significant ketones.
- Search for and treat the precipitating cause of the patient's HHS.
- Fluid resuscitation and subsequent continuous infusion of intravenous fluids and insulin are the recommended treatments for HHS.
- Serum glucose should be kept greater than 250 mg/dL and closer to 300 mg/dL during the treatment of HHS to minimize the risk of cerebral edema.
- Frequent reassessment of the patient's mental status, volume status, renal function, electrolytes, serum osmolarity, and serum glucose are required to minimize the risk of complications.

DISCLOSURES

The authors have nothing to disclose.

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